

# PATENT SPECIFICATION

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1311573

## NO DRAWINGS

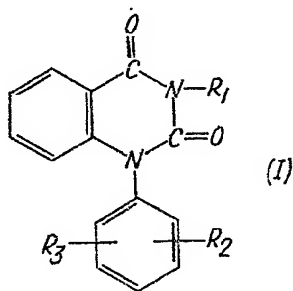
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## (54) QUINAZOLINEDIONE DERIVATIVES

(71) We, HISAMITSU PHARMA-  
 CEUTICAL COMPANY, INC., a Japanese  
 company of 408, Tashiro, Tosu City, Saga  
 Prefecture, Japan, do hereby declare the in-  
 vention, for which we pray that a patent may  
 be granted to us, and the method by which it  
 is to be performed, to be particularly described  
 in and by the following statement:—

The present invention relates to novel quin-  
 azolinedione derivatives and process for the  
 production of the same, and, more particularly,  
 to quinazolinedione derivatives and process  
 for the production thereof expressed in the  
 following general formula:



15

wherein R<sub>1</sub> represents an alkyl, a substituted  
 alkyl or an acyl radical; R<sub>2</sub> and R<sub>3</sub> each rep-  
 resent a hydrogen atom, a CF<sub>3</sub> group, a Cl, Br,  
 or F atom, or a methyl, methoxy or ethoxy  
 radical.

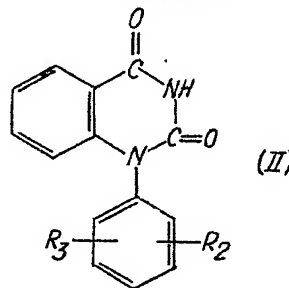
Conventionally, Aminopyrine, Mefenamic  
 acid, Flufenamic acid and others were known  
 as an anti-inflammatory and an analgesic,  
 however, they possessed the disadvantage of  
 causing gastroenteric trouble. We have found

that these novel quinazolinedione derivatives  
 have excellent anti-inflammatory action and  
 analgesic action, as described later, without  
 causing gastroenteric trouble.

Thus, one of the objects of the present in-  
 vention is to provide the novel quinazoline-  
 dione derivatives having the excellent anti-  
 inflammatory action and analgesic action.

Further, another object of the present in-  
 vention is to provide the process for producing  
 such novel quinazolinedione derivatives in  
 high yield and advantageously.

According to the present invention, the  
 aforesaid quinazolinedione derivatives are pro-  
 duced by reacting a compound of formula:



(wherein R<sub>2</sub> and/or R<sub>3</sub> represent the same as  
 mentioned above) with an alkylating or acylat-  
 ing agent containing the group R<sub>1</sub>, as defined  
 above, e.g. a compound of formula R<sub>1</sub>X  
 (wherein R<sub>1</sub> is as defined above and X repre-  
 sents a halogen atom, or with a compound of  
 formula (R)<sub>2</sub>SO<sub>3</sub>, wherein R represents a  
 methyl or ethyl group, as alkylating agent.  
 Consequently, the reaction of the present in-  
 vention can be understood as being alkylation  
 or acylation.

[P

The abovementioned compounds used as starting reaction materials in the present invention can be obtained in good yield by reacting N-phenylanthranilic acid or N-substituted phenylanthranilic acid with urea.

5 The quinazolinedione derivatives used as the aforesaid starting reaction materials include 1 - phenyl - 2,4(1H, 3H) - quinazolin-  
10 dione or 1 - substituted phenyl - 2,4(1H, 3H) - quinazolinedione, for example, 1 - (3' - trifluoromethylphenyl) - 2,4(1H, 3H) - quin-  
15 azolinedione, 1 - (3' - chlorophenyl) - 2,4-(1H, 3H) - quinazolinedione, 1 - (2',3' - dichlorophenyl) - 2,4(1H, 3H) - quinazolin-  
20 edione, 1 - (2' - chlorophenyl) - 2,4(1H, 3H) - quinazolinedione, 1 - (4' - chlorophenyl) - 2,4(1H, 3H) - quinazolin-  
30 edione, 1 - (3',4' - dichlorophenyl) - 2,4(1H, 3H) - quinazolin-  
35 edione, 1 - (2',6' - dichlorophenyl) - 2,4-(1H, 3H) - quinazolin-  
40 edione, 1 - (3' - fluorephenyl) - 2,4(1H, 3H) - quinazolin-  
45 edione, 1 - (4' - fluorephenyl) - 2,4(1H, 3H) - quinazolin-  
50 edione, 1 - (3' - bromophenyl) - 2,4(1H, 3H) - quinazolin-  
55 edione, 1 - (2',3' - dimethylphenyl) - 2,4(1H, 3H) - quinazolin-  
60 edione, 1 - (3' - methoxyphenyl) - 2,4(1H, 3H) - quin-  
azolin-  
edione, 1 - (4' - ethoxyphenyl) - 2,4-(1H, 3H) - quinazolin-  
edione and 1 - (3' - methylphenyl) - 2,4(1H, 3H) - quinazolin-  
edione.

In the group of compounds used as alkylating or acylating agent of the abovementioned starting reaction materials in the present invention expressed by the general formula  $R_1X$ ,  $R_1$  can for example, either be saturated or unsaturated alkyl or alkyl radical substituted by aryl-, halogen-, hydroxy-, amino-, alkoxy-, alkylthio-, phenoxy-, acyloxy-, acyl-, carbamoyloxy- or carbamoylalkoxy-radical, and said compounds include, for example, ethyl iodide, n-butyl bromide, iso-amyl iodide, benzyl bromide, 1-bromo-2-chloroethane, 2-diethylaminoethyl chloride, ethylene bromohydrin, chloromethyl ethyl ether, 2-bromoethyl acetate, 1-chloro-2-(N,N-dimethylcarbamoyloxy)-ethane, p-chlorobenzoyl chloride, acetyl chloride, benzoyl chloride, propionyl chloride, dimethylamino-propyl chloride, 2-bromoethyl ethyl ether and 2-bromoethyl benzoate. Further, the other group of compounds used as alkylating agent same as above is expressed by the general formula  $(R)_2SO_2$ , wherein R can be methyl or ethyl radical, dimethyl sulfate being more typical.

60 The reaction in the present invention is preferred to be performed in the presence of

metallic compounds such as a sodium alcoholate, sodamide and sodium hydride, organic base such as pyridine and trialkylamine, or inorganic base such as alkali hydroxide and alkali carbonate.

Further, since the reaction of the present invention is usually made in an organic solvent such as acetone or dimethylformamide, it is carried out at a wide range of temperature. Consequently, the reaction temperature is not critical but can be either normal, warm or cool.

The compounds obtained according to the present invention show significant anti-inflammatory action and analgesic action as is apparent from the experimental tests as set forth below.

According to a further feature of the present invention, there are provided pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I, as defined above, in association with at least one pharmaceutically acceptable vehicle, diluent, excipient, or carrier.

Tests have been performed on acute toxicity, anti-inflammatory effect and analgesic effect of the invented compounds.

#### Testing Method of Acute Toxicity

Tragacanth emulsion was given intraperitoneally to healthy dd mice of 15 to 20g, and  $LD_{50}$  and its 95% confidence limits were calculated by Litchfield-Wilcoxon method from the lethal number after 72 hours.

#### Testing Method of Anti-inflammatory Effect

The drugs subjected to this test were given intragastrically to healthy female Wistar rats of 100 to 140 g, the inflammatory substance, carrageenin (1%, 0.1 ml), was injected subcutaneously into the soles of the rats' hind legs after 60 minutes, and the inhibition rates (%) against edema were measured by comparing the edema consequently arisen to the tested rats with the controls to which the drugs were not given. The amount of drugs given was 200 mg/kg and the mean inhibition rates were shown of 4 to 5 rats in a group.

In performing the above test, not only the compounds obtained by the present invention were employed, but the conventionally known compounds such as Mefenamic acid and Flufenamic acid were also subjected to the same test. The comparisons between the former and the latter were shown in the following table.

|   | Compounds  | Acute Toxicity                             | Anti-inflammatory   |
|---|--|--|---|
|   |  | LD <sub>50</sub><br>mg/kg i.p. 95%<br>C.L. | Effect Inhibition<br>Rates Against<br>Edema Induced by<br>Carrageenin |
| Test<br>Examples of<br>the<br>Compounds<br>Obtained<br>by the<br>Present<br>Invention | 1-(3'-trifluoromethylphenyl)-<br>3-methyl-2,4(1H, 3H)-<br>quinazolinedione                                   | 360 (340—381)                              | +++   |
|   | 1-(3'-trifluoromethylphenyl)-<br>3-ethyl-2,4(1H, 3H)-<br>quinazolinedione                                    | 373 (341)—408)                             | ++++  |
|   | 1-(3'-trifluoromethyl)-3-<br>(2''-chloroethyl)-2,4(1H, 3H)-<br>quinazolinedione                              | > 800                                      | +++   |
|   | 1-(3'-trifluoromethylphenyl)-<br>3-(2''-diethylaminoethyl)-<br>2,4(1H, 3H)-quinazolinedione<br>hydrochloride | 158 (137—182)                              | ++++  |
|   | 1-(3'-trifluoromethylphenyl)-<br>3-(2''-hydroxyethyl)-2,4-<br>(1H, 3H)-quinazolinedione                      | 253 (220—291)                              | ++++  |
|   | 1-(3'-trifluoromethylphenyl)-<br>3-(2''-ethoxyethyl)-2,4-<br>(1H, 3H)-quinazolinedione                       | 460 (430—492)                              | ++++  |
|   | 1-(3'-trifluoromethylphenyl)-<br>3-(2''-acetoxyethyl)-2,4-<br>(1H, 3H)-quinazolinedione                      | > 400                                      | +++   |
|   | 1-(3'-chlorophenyl)-3-ethyl-<br>2,4(1H, 3H)-quinazolinedione   | > 800                                      | ++++  |
|   | 1-(3'-chlorophenyl)-3-(2''-<br>hydroxyethyl)-2,4(1H, 3H)-<br>quinazolinedione                                | > 400                                      | ++++  |
|   | 1,3'-fluorophenyl)-3-ethyl-2,4-<br>(1H, 3H)-quinazolinedione   | > 400                                      | ++++  |
| Comparison  | Mefenamic acid   | 420 (395—458)                              | +++   |
|   | Flufenamic acid  | 200 (180—222)                              | +++   |

In the above table +++ shows that the mean inhibition rate is 30 — 39%, and ++++ shows that said rate is more than 40%.

#### Testing Method of Analgesic Effect Morphinized Haffner Method

5 The test was performed by employing healthy male dd-mice of 15—17 g, a single group consisted of 10 mice, with regard to inhibition of "withdrawal" against pressing at the root of the tail using in combination with the threshold dose (2.5 mg/kg s.c.) of Mor-

phine hydrochloride. The test drugs had been 10 given intragastrically 30 minutes before morphine was given, and ED<sub>50</sub> and 95% confidence limits were calculated by Litchfield-Wilcoxon method from its result.

#### Acetic Acid Stretching Method

15 This test was performed by employing

5 healthy male dd mice of 15—17 g, a single group consisted of 6 to 8 mice, with regard to inhibition of stretching (or squirm) symptoms induced by intraperitoneal injection 0.1 ml/10 g of 0.6% acetic acid. The test drugs had been given intragastrically 30 minutes before acetic acid was given, and ED<sub>50</sub> and 95% confidence limits were calculated by Litchfield-Wilcoxon method from its result.




10 In performing the above test, not only the compounds obtained by the present invention were employed, but the conventionally known compounds such as Mefenamic acid, Flufenamic acid and Aminopyrine were also subjected to the same test.

-- The comparison between the former and the latter is shown in the following table.

| Compounds  | Testing Method  |  |
|--|---|--|
|  | Acetic Acid Stretching method<br>ED <sub>50</sub> =mg/kg P.O.<br>(C.L. 95%)     | Morphinized Haffner method<br>ED <sub>50</sub> =mg/kg P.O.<br>(C.L. 95%) |
| Test Examples of the Compounds Obtained by the Present Invention | 1-(3'-trifluoromethylphenyl)-3-ethyl-2,4(1H, 3H)-quinazolinedione               | 100>33% Peak 148 (135—163)   |
|  | 1-(3'-trifluoromethylphenyl)-3-(2''-hydroxyethyl)-2,4-(1H, 3H)-quinazolinedione | 35 (28—43) 38 (26—54)  |
|  | 1-(3'-trifluoromethylphenyl)-3-(2''-ethoxyethyl)-2,4(1H, 3H)-quinazolinedione   | 200>60% Peak 100>60% Peak  |
|  | 1-(3'-trifluoromethylphenyl)-3-(2''-acetoxyethyl)-2,4-(1H, 3H)-quinazolinedione | 94 (70—126) 124 (114—135)  |
|  | 1-(3'-chlorophenyl)-3-ethyl-2,4(1H, 3H)-quinazolinedione                        | 167 (140—223) 100>60% Peak   |
|  | 1-(3'-chlorophenyl)-3-(2''-hydroxyethyl)-2,4(1H, 3H)-quinazolinedione           | 56 (44—72) 75>55% Peak   |
|  | 1-(3'-chlorophenyl)-3-(2''-ethoxyethyl)-2,4(1H, 3H)-quinazolinedione            | 82 (50—134) 130>50% Peak   |
|  | 1-(3'-chlorophenyl)-3-(2''-acetoxyethyl)-2,4(1H, 3H)-quinazolinedione           | 65 (45—94) 75>60% Peak   |
| Comparison   | Aminopyrine   | 93 (60—143) 65 (45—94)   |
|  | Mefenamic Acid  | 134 (100—180) 140 (114—172)  |
|  | Flufenamic Acid   | 170 (121—238) 200>35% Peak   |

20 The following examples are given for illustrating the invention.  
*Examples of quinazolinedione derivatives produced according to the present invention:—*

|    | *I<br>R X   | product  |                               |                           |                  |
|----|---|--|-------------------------------|---------------------------|------------------|
|    |   | molecular formula  | m.p. or b.p. (°C).            | recrystallization solvent | appearance       |
| 1  | $\text{Br}-\text{CH}_2-\text{CH}_2-\text{CH}_3$                                     | $\text{C}_{18}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_2$   | m.p. 153                      | methanol                  | colorless prisms |
| 2  | $\text{Br}-\text{CH}(\text{CH}_3)_2$  | $\text{C}_{18}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_2$   | m.p. 131—3                    | "                         | "                |
| 3  | $\text{Br}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$                                    | $\text{C}_{19}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_2$   | m.p. 111—3                    | "                         | "                |
| 4  | $\text{Br}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3$             | $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_2$   | m.p. 102—3                    | "                         | "                |
| 5  | $\text{Br}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3$ | $\text{C}_{21}\text{H}_{21}\text{F}_3\text{N}_2\text{O}_2$   | m.p. 77—8                     | "                         | "                |
| 6  | $\text{Br}-\text{CH}_2-\text{CH}=\text{CH}_2$                                       | $\text{C}_{18}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_2$   | m.p. 123—4                    | "                         | "                |
| 7  | $\text{Cl}-\text{CH}_2-\text{C}_6\text{H}_4-\text{Cl}$                              | $\text{C}_{22}\text{H}_{14}\text{ClF}_3\text{N}_2\text{O}_2$ | m.p. 196—7                    | ethanol                   | "                |
| 8  | $\text{Cl}-\text{CH}_2-\text{C}_6\text{H}_4-\text{OCH}_3$                           | $\text{C}_{23}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_3$   | m.p. 203—4                    | "                         | "                |
| 9  | $\text{Br}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{Cl}$                           | $\text{C}_{18}\text{H}_{14}\text{ClF}_3\text{N}_2\text{O}_2$ | m.p. 134—5                    | methanol                  | "                |
| 10 | $\text{Cl}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_2$                         | $\text{C}_{19}\text{H}_{19}\text{ClF}_3\text{N}_2\text{O}_2$ | m.p. 137—8<br>(hydrochloride) | ethanol + n-hexane        | "                |



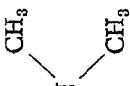
|    | *1<br>R X   | product  |                                 |                           |                    |
|----|---|--|---------------------------------|---------------------------|--------------------|
|    |   | molecular formula  | m.p. or b.p. (°C).              | recrystallization solvent | appearance         |
| 11 | $\text{Cl}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_2$   | $\text{C}_{10}\text{H}_{21}\text{ClF}_3\text{N}_3\text{O}_2$ | m.p. 245<br>(hydrochloride)     | ethyl acetate             | colorless prisms   |
| 12 | $\text{Cl}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}(\text{C}_2\text{H}_5)_2$  | $\text{C}_{22}\text{H}_{25}\text{ClF}_3\text{N}_3\text{O}_2$ | m.p. 225—6<br>(hydrochloride)   | "                         | "                  |
| 13 | $\text{Cl}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}(\text{C}_2\text{H}_5)_2$<br>   | $\text{C}_{22}\text{H}_{23}\text{ClF}_3\text{N}_3\text{O}_2$ | m.p. 180—1<br>(hydrochloride)   | "                         | "                  |
| 14 | $\text{Cl}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_2$<br>           | $\text{C}_{23}\text{H}_{27}\text{ClF}_3\text{N}_4\text{O}_2$ | m.p. 272—3<br>(dihydrochloride) | ethanol                   |                    |
| 15 | $\text{Cl}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}(\text{C}_2\text{H}_5)_2$<br> | $\text{C}_{23}\text{H}_{25}\text{ClF}_3\text{N}_3\text{O}_2$ | m.p. 252—3<br>(hydrochloride)   | chloroform<br>+ n-hexane  | pale yellow prisms |
| 16 | $\text{Cl}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{OH}$   | $\text{C}_{18}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_3$   | m.p. 106—7                      | methanol                  | colorless prisms   |
| 17 | $\text{Cl}-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-\text{OH}$  | $\text{C}_{18}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_4$   | m.p. 154—5.5                    | ethanol                   | "                  |

|    | *I<br>R X   | product  |                    |                           |                  |
|----|---|--|--------------------|---------------------------|------------------|
|    |   | molecular formula  | m.p. or b.p. (°C.) | recrystallization solvent | appearance       |
| 18 | $\text{Cl}-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_3$          | $\text{C}_{19}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_3$ | m.p. 11.7—8        | methanol                  | colorless prisms |
| 19 | $\text{Cl}-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$                      | $\text{C}_{13}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_3$ | b.p. 205           | —                         | pale yellow oil  |
| 20 | $\text{Cl}-\text{CH}_2-\text{CH}_2-\text{O}-\text{C}_6\text{H}_5$             | $\text{C}_{23}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_3$ | m.p. 155—6         | methanol                  | colorless prisms |
| 21 | $\text{Cl}-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_2-\text{C}_6\text{H}_5$ | $\text{C}_{24}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_3$ | b.p. 235           | —                         | pale yellow oil  |
| 22 | $\text{Cl}-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}=\text{CH}_2$            | $\text{C}_{19}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_3$ | m.p. 127—5—8.5     | methanol                  | colorless prisms |
| 23 | $\text{Cl}-\text{CH}_2-\text{CH}_2-\text{O}-\text{COC}_2\text{H}_5$           | $\text{C}_{20}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_4$ | m.p. 104—5         | ”                         | ”                |
| 24 | $\text{Cl}-\text{CH}_2-\text{CH}_2-\text{O}-\text{CO}-\text{C}_6\text{H}_5$   | $\text{C}_{24}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_4$ | m.p. 150—1         | ”                         | ”                |
| 25 | $\text{Cl}-\text{CH}_2-\text{COCH}_3$   | $\text{C}_{18}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_3$ | m.p. 184—5         | ”                         | ”                |

|    | *I<br>R X  | product  |                    |                              |                  |
|----|--|--|--------------------|------------------------------|------------------|
|    |  | molecular formula  | m.p. or b.p. (°C.) | recrystallization solvent    | appearance       |
| 26 | <br>$\text{Cl}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{N}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{C}_6\text{H}_4-\text{F}_3\text{C}$                                  | $\text{C}_{32}\text{H}_{20}\text{F}_6\text{N}_4\text{O}_4$         | m.p. 132—2.5       | dimethylformamide<br>+ water | colorless prisms |
| 27 | <br>$\text{Cl}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_2-\text{N}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{N}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{C}_6\text{H}_4-\text{F}_3\text{C}$ | $\text{C}_{34}\text{H}_{17}\text{F}_6\text{N}_4\text{O}_5$         | m.p. 222—3         | methanol + ethyl acetate     | ”                |
| 28 | $\text{Cl}-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$   | $\text{C}_{19}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_3\text{S}$ | m.p. 90—1          | methanol                     | ”                |
| 29 | $\text{Cl}-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_2-\text{CONH}_2$   | $\text{C}_{19}\text{H}_{16}\text{F}_3\text{N}_3\text{O}_4$         | m.p. 153—4         | ”                            | ”                |

The asterisk I shown in the above table represents the general formula of the compounds to be reacted with the above-mentioned 1-(3'-trifluoromethylphenyl)-2,4(1H,3H)-quinazolinone in the process of the present invention.



|    | *II<br>R X   | product  |                    |                           |                   |
|----|--|--|--------------------|---------------------------|-------------------|
|    |  | molecular formula  | m.p. or b.p. (°C.) | recrystallization solvent | appearance        |
| 30 | $\text{ClCOCH}_2\text{CH}_3$   | $\text{C}_{18}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_3$   | m.p. 177.5—8.5     | methanol                  | colorless needles |
| 31 | $\text{BrCH}_2\text{CH}_2\text{Br}$  | $\text{C}_{17}\text{H}_{12}\text{BrF}_3\text{N}_2\text{O}_2$ | m.p. 144.5—5.5     | „                         | colorless prisms  |
| 32 | $\text{ClCH}_2\text{CH}_2$      | $\text{C}_{23}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_2$   | m.p. 122.5—3.5     | „                         | colorless needles |
| 33 | $\text{CH}_3$<br>$\text{CfCH}$  | $\text{C}_{23}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_2$   | m.p. 142.5—3.5     | „                         | colorless prisms  |
| 34 | $\text{Br CH CH O CON}$        | $\text{C}_{20}\text{H}_{18}\text{F}_3\text{N}_2\text{O}_4$   | m.p. 157—8         | „                         | „                 |

The asterisk II shown in the above table represents the general formula of the compounds to be reacted with the above-mentioned 1-(3'-trifluoromethylphenyl)-2,4-(1H,3H)-quinazolinone.

|    | *III<br>R X                                       | product   |                    |                           |                  |
|----|---|---|--------------------|---------------------------|------------------|
|    |   | molecular formula                                   | m.p. or b.p. (°C.) | recrystallization solvent | appearance       |
| 35 | $\text{BrCH}_2\text{CH}_2\text{OCOCCH}_3$         | $\text{C}_{15}\text{H}_{15}\text{F N}_2\text{O}_4$  | m.p. 115.5—6.5     | methanol                  | colorless prisms |
| 36 | $\text{I CH}_2\text{CH}_3$                        | $\text{C}_{16}\text{H}_{13}\text{FN}_2\text{O}_2$   | m.p. 147.5—8.5     | „                         | „                |
| 37 | $\text{BrCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ | $\text{C}_{18}\text{H}_{17}\text{FN}_2\text{O}_3$   | m.p. 109—10        | „                         | „                |
| 38 | $\text{BrCH}_2\text{CH}_2\text{Cl}$               | $\text{C}_{16}\text{H}_{12}\text{ClFN}_2\text{O}_2$ | m.p. 185.5—6.5     | „                         | „                |

The asterisk III shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(3'-fluorophenyl)-2,4(1H,3H)-quinazolinone.

|    | *IV<br>R X  | product  |                    |                           |                    |
|----|---|--|--------------------|---------------------------|--------------------|
|    |   | molecular formula                                    | m.p. or b.p. (°C.) | recrystallization solvent | appearance         |
| 39 | $\text{I CH}_2\text{CH}_3$                        | $\text{C}_{16}\text{H}_{13}\text{BrN}_2\text{O}_2$   | m.p. 187.5—8.5     | ethanol                   | colorless prisms   |
| 40 | $\text{BrCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ | $\text{C}_{18}\text{H}_{17}\text{BrN}_2\text{O}_3$   | m.p. 155—7         | methanol                  | „                  |
| 41 | $\text{BrCH}_2\text{CH}_2\text{OH}$               | $\text{C}_{16}\text{H}_{13}\text{BrN}_2\text{O}_3$   | m.p. 161.5—2.0     | methanol + water          | „                  |
| 42 | $\text{BrCH}_2\text{CH}_2\text{Cl}$               | $\text{C}_{16}\text{H}_{12}\text{ClBrN}_2\text{O}_2$ | m.p. 184—6         | dimethylformamide         | pale yellow prisms |

The asterisk IV shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(3'-bromophenyl)-2,4(1H,3H)-quinazolinone.

|    | * V<br>R X   | product   |                    |                              |                    |
|----|--|---|--------------------|------------------------------|--------------------|
|    |  | molecular formula   | m.p. or b.p. (°C.) | recrystallization solvent    | appearance         |
| 43 | BrCH <sub>2</sub> CH <sub>2</sub> OCOCH <sub>3</sub>               | C <sub>20</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub> | m.p. 181—3         | methanol + dimethylformamide | pale yellow prisms |
| 44 | BrCH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>3</sub> | C <sub>20</sub> H <sub>22</sub> N <sub>2</sub> O <sub>3</sub> | m.p. 104—6         | methanol                     | colorless needles  |

The asterisk V shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(2',3'-dimethylphenyl)-2,4(1H,3H)-quinazolinone.

|    | *VI<br>R X   | product  |                    |                              |                  |
|----|--|--|--------------------|------------------------------|------------------|
|    |  | molecular formula  | m.p. or b.p. (°C.) | recrystallization solvent    | appearance       |
| 45 | ICH <sub>2</sub> CH <sub>3</sub>                     | C <sub>16</sub> H <sub>13</sub> FN <sub>2</sub> O <sub>2</sub>   | m.p. 213—5         | methanol + dimethylformamide | colorless prisms |
| 46 | BrCH <sub>2</sub> CH <sub>2</sub> OCOCH <sub>3</sub> | C <sub>18</sub> H <sub>15</sub> FN <sub>2</sub> O <sub>4</sub>   | m.p. 144—6         | methanol                     | "                |
| 47 | BrCH <sub>2</sub> CH <sub>2</sub> Cl                 | C <sub>16</sub> H <sub>12</sub> ClFN <sub>2</sub> O <sub>2</sub> | m.p. 205—8         | dimethylformamide            | "                |

The asterisk VI shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(4'-fluorophenyl)-2,4(1H,3H)-quinazolinone.

|    | * VII<br>R X   | product   |                    |                              |                  |
|----|--|---|--------------------|------------------------------|------------------|
|    |  | molecular formula   | m.p. or b.p. (°C.) | recrystallization solvent    | appearance       |
| 48 | ICH <sub>2</sub> CH <sub>3</sub>                                   | C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> | m.p. 139.5—40.5    | methanol                     | colorless prisms |
| 49 | BrCH <sub>2</sub> CH <sub>2</sub> OCOCH <sub>3</sub>               | C <sub>19</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub> | m.p. 150—1         | methanol + dimethylformamide | "                |
| 50 | BrCH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>3</sub> | C <sub>19</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> | m.p. 136—7         | methanol                     | "                |

The asterisk VII shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(3'-methylphenyl)-2,4(1H,3H)-quinazolinone.

|    | * VIII<br>R X                    | product   |                    |                           |                  |
|----|----------------------------------|---|--------------------|---------------------------|------------------|
|    |                                  | molecular formula   | m.p. or b.p. (°C.) | recrystallization solvent | appearance       |
| 51 | ICH <sub>2</sub> CH <sub>3</sub> | C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> | m.p. 164—5         | methanol                  | colorless prisms |

The asterisk VIII shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(3'-methoxyphenyl)-2,4(1H,3H)-quinazolinone.

|    | * IX<br>R X  | product   |                    |                             |                  |
|----|--|---|--------------------|-----------------------------|------------------|
|    |  | molecular formula   | m.p. or b.p. (°C.) | recrystallization solvent   | appearance       |
| 52 | ICH <sub>2</sub> CH <sub>3</sub>                                   | C <sub>18</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub> | m.p. 191—3         | ethanol + dimethylformamide | colorless prisms |
| 53 | BrCH <sub>2</sub> CH <sub>2</sub> OCOCH <sub>3</sub>               | C <sub>20</sub> H <sub>20</sub> N <sub>2</sub> O <sub>5</sub> | m.p. 134.5—5.5     | methanol                    | "                |
| 54 | BrCH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>3</sub> | C <sub>20</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub> | m.p. 136—8         | "                           | "                |
| 55 | BrCH <sub>2</sub> CH <sub>2</sub> OH                               | C <sub>18</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub> | m.p. 166.5—8.0     | "                           | "                |

The asterisk IX shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(4'-methoxyphenyl)-2,4(1H,3H)-quinazolinone.

|    | * X<br>R X   | product   |                    |                           |                    |
|----|--|---|--------------------|---------------------------|--------------------|
|    |  | molecular formula   | m.p. or b.p. (°C.) | recrystallization solvent | appearance         |
| 56 | ICH <sub>2</sub> CH <sub>3</sub>                                   | C <sub>16</sub> H <sub>13</sub> ClN <sub>3</sub> O <sub>2</sub> | m.p. 160—3         | methanol                  | colorless prisms   |
| 57 | ICH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>   | C <sub>18</sub> H <sub>17</sub> ClN <sub>3</sub> O <sub>2</sub> | m.p. 144—5         | "                         | colorless needles  |
| 58 | BrCH <sub>2</sub> CH <sub>2</sub> OCOCH <sub>3</sub>               | C <sub>18</sub> H <sub>15</sub> ClN <sub>3</sub> O <sub>4</sub> | m.p. 145—7         | ethanol                   | pale yellow prisms |
| 59 | BrCH <sub>2</sub> CH <sub>2</sub> Cl                               | C <sub>16</sub> H <sub>13</sub> ClN <sub>3</sub> O <sub>2</sub> | m.p. 169—70        | "                         | colorless prisms   |
| 60 | BrCH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>3</sub> | C <sub>18</sub> H <sub>17</sub> ClN <sub>3</sub> O <sub>3</sub> | m.p. 134—6         | methanol                  | "                  |
| 61 | ClCH <sub>2</sub> COOCH <sub>2</sub> CH <sub>3</sub>               | C <sub>18</sub> H <sub>15</sub> ClN <sub>3</sub> O <sub>4</sub> | m.p. 181—3         | ethanol                   | colorless needles  |
| 62 | BrCH <sub>2</sub> CH <sub>2</sub> OH                               | C <sub>16</sub> H <sub>13</sub> ClN <sub>3</sub> O <sub>2</sub> | m.p. 145—6         | methanol                  | "                  |

The asterisk X shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(4'-chlorophenyl)-2,4(1H,3H)-quinazolinedione.

|    | * XI<br>R X  | product   |                    |                           |                   |
|----|--|---|--------------------|---------------------------|-------------------|
|    |  | molecular formula   | m.p. or b.p. (°C.) | recrystallization solvent | appearance        |
| 63 | BrCH <sub>2</sub> CH <sub>2</sub> OCOCH <sub>3</sub>               | C <sub>18</sub> H <sub>15</sub> ClN <sub>3</sub> O <sub>4</sub> | m.p. 144—5         | methanol                  | colorless prisms  |
| 64 | BrCH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>3</sub> | C <sub>18</sub> H <sub>17</sub> ClN <sub>3</sub> O <sub>3</sub> | m.p. 129—30        | "                         | colorless needles |
| 65 | BrCH <sub>2</sub> CH <sub>2</sub> OH                               | C <sub>16</sub> H <sub>13</sub> ClN <sub>3</sub> O <sub>2</sub> | m.p. 149—52        | "                         | colorless prisms  |

The asterisk XI shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(2'-chlorophenyl)-2,4(1H,3H)-quinazolinedione.

|    | * XII<br>R X  | product   |                    |                           |                   |
|----|---|---|--------------------|---------------------------|-------------------|
|    |   | molecular formula   | m.p. or b.p. (°C.) | recrystallization solvent | appearance        |
| 66 | $\text{ICH}_2\text{CH}_3$   | $\text{C}_{16}\text{H}_{13}\text{ClN}_2\text{O}_2$          | m.p. 179—80        | ethanol                   | colorless prisms  |
| 67 | $\text{BrCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$   | $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_3$          | m.p. 115—6         | "                         | "                 |
| 68 | $\text{BrCH}_2\text{CH}_2\text{OCOCH}_3$  | $\text{C}_{18}\text{H}_{15}\text{ClN}_2\text{O}_4$          | m.p. 136—7         | methanol                  | "                 |
| 69 | $\text{BrCH}_2\text{CH}_2\text{OH}$   | $\text{C}_{15}\text{H}_{13}\text{ClN}_2\text{O}_3$          | m.p. 149.0—50.5    | "                         | "                 |
| 70 | $\text{BrCH}_2\text{CH}_2\text{CH}_2\text{OH}$  | $\text{C}_{17}\text{H}_{15}\text{ClN}_2\text{O}_3$          | m.p. 136.5—9.5     | "                         | "                 |
| 71 | $\text{ClCH}_2\text{COOCH}_2\text{CH}_3$  | $\text{C}_{18}\text{H}_{15}\text{ClN}_2\text{O}_4$          | m.p. 127—9         | "                         | "                 |
| 72 | $\text{BrCH}_2\text{CH}_2\text{Cl}$   | $\text{C}_{16}\text{H}_{12}\text{Cl}_2\text{N}_2\text{O}_2$ | m.p. 170—1         | "                         | "                 |
| 73 | $\text{ICH}_2\text{CH}_2\text{CH}_2\text{CH}_3$   | $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_2$          | m.p. 141—6         | "                         | "                 |
| 74 | $\begin{array}{c} \text{CH}_3 \\   \\ \text{BrCH}_2\text{CH} \\   \\ \text{CH}_3 \end{array}$ | $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_2$          | m.p. 121—3         | "                         | "                 |
| 75 | $\text{ClCH}_2\text{CH}_2\text{CH}_3$   | $\text{C}_{17}\text{H}_{15}\text{ClN}_2\text{O}_2$          | m.p. 132—4         | "                         | "                 |
| 76 | $\begin{array}{c} \text{CH}_3 \\   \\ \text{ICH} \\   \\ \text{CH}_3 \end{array}$             | $\text{C}_{17}\text{H}_{15}\text{ClN}_2\text{O}_2$          | m.p. 140.0—1.5     | "                         | colorless needles |

The asterisk XII shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(3'-chlorophenyl)-2,4(1H,3H)-quinazolinone.

|    | * XIII<br>R X                                     | product   |                    |                           |                   |
|----|---|---|--------------------|---------------------------|-------------------|
|    |   | molecular formula   | m.p. or b.p. (°C.) | recrystallization solvent | appearance        |
| 77 | $\text{ICH}_2\text{CH}_3$                         | $\text{C}_{16}\text{H}_{13}\text{Cl}_2\text{N}_2\text{O}_2$ | m.p. 166.0—7.5     | methanol                  | colorless prisms  |
| 78 | $\text{BrCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ | $\text{C}_{18}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_3$ | m.p. 102.5—4.0     | "                         | "                 |
| 79 | $\text{BrCH}_2\text{CH}_2\text{OH}$               | $\text{C}_{16}\text{H}_{12}\text{Cl}_2\text{N}_2\text{O}_3$ | m.p. 144.5—6.0     | methanol + water          | colorless needles |

The asterisk XIII shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(2',3'-dichlorophenyl)-2,4(1H,3H)-quinazolinedioxc.

|    | * XIV<br>R X                                      | product   |                    |                             |                    |
|----|---|---|--------------------|-----------------------------|--------------------|
|    |   | molecular formula   | m.p. or b.p. (°C.) | recrystallization solvent   | appearance         |
| 80 | $\text{ICH}_2\text{CH}_3$                         | $\text{C}_{16}\text{H}_{12}\text{Cl}_2\text{N}_2\text{O}_3$ | m.p. 139—41        | methanol                    | colorless prisms   |
| 81 | $\text{BrCH}_2\text{CH}_2\text{OCOCH}_3$          | $\text{C}_{18}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O}_4$ | m.p. 120—1         | "                           | colorless needles  |
| 82 | $\text{BrCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$ | $\text{C}_{18}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_3$ | m.p. 114.0—5.5     | "                           | "                  |
| 83 | $\text{BrCH}_2\text{CH}_2\text{OH}$               | $\text{C}_{16}\text{H}_{12}\text{Cl}_2\text{N}_2\text{O}_3$ | m.p. 145—7         | "                           | pale yellow prisms |
| 84 | $\text{BrCH}_2\text{CH}_2\text{Cl}$               | $\text{C}_{16}\text{H}_{11}\text{Cl}_3\text{N}_2\text{O}_2$ | m.p. 155—6         | ethanol + dimethylformamide | colorless prisms   |

The asterisk XIV shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(3',4'-dichlorophenyl)-2,4(1H,3H)-quinazolinedioxc.

|    | * XV<br>R X  | product  |                    |                           |                    |
|----|--|--|--------------------|---------------------------|--------------------|
|    |  | molecular formula                                  | m.p. or b.p. (°C.) | recrystallization solvent | appearance         |
| 85 | $\text{ICH}_2\text{CH}_3$  | $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2$   | m.p. 196.5—7.5     | ethanol                   | colorless prisms   |
| 86 | $\text{ICH}_2\text{CH}_2\text{CH}_2\text{CH}_3$                                  | $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2$   | m.p. 106—7         | methanol + water          | "                  |
| 87 | $\text{ClCH}_2\text{COOCH}_2\text{CH}_3$   | $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_4$   | m.p. 164—5         | methanol                  | "                  |
| 88 | $\text{BrCH}_2\text{CH}_2\text{OH}$  | $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3$   | m.p. 205.5—8.0     | "                         | "                  |
| 89 | $\text{BrCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$                                | $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3$   | m.p. 93—5          | "                         | "                  |
| 90 | $\text{BrCH}_2\text{CH}_2\text{OCOCH}_3$   | $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_4$   | m.p. 159—60.5      | "                         | "                  |
| 91 | $\text{BrCH}_2\text{CH}_2\text{Cl}$  | $\text{C}_{16}\text{H}_{13}\text{ClN}_2\text{O}_2$ | m.p. 214.0—6.5     | dimethylformamide         | "                  |
| 92 | $\text{BrCH}_2\text{CH}_2\text{CH}_2\text{Cl}$                                   | $\text{C}_{17}\text{H}_{15}\text{ClN}_2\text{O}_2$ | m.p. 153—4         | methanol                  | pale yellow prisms |
| 93 | $\begin{array}{c} \text{CH}_3 \\   \\ \text{ClCHCOOCH}_2\text{CH}_3 \end{array}$ | $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_4$   | m.p. 129—30        | "                         | "                  |
| 94 | $\text{BrCH}_2\text{OCH}_2\text{CONH}_2$   | $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_4$   | m.p. 159.5—60.5    | "                         | yellow needles     |
| 95 | $\text{ClCH}_2\text{CH}_2\text{O}-\text{C}_6\text{H}_5$                          | $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_3$   | m.p. 188—9         | dimethylformamide         | colorless needles  |



|    | * XV<br>R X | product                |                    |                              |                  |
|----|-------------|------------------------|--------------------|------------------------------|------------------|
|    |             | molecular formula      | m.p. or b.p. (°C.) | recrystallization solvent    | appearance       |
| 96 |             | $C_{23}H_{15}ClN_4O_4$ | m.p. 179—80        | methanol                     | 23               |
| 97 |             | $C_{22}H_{18}N_2O_3$   | m.p. 178—9         | methanol + dimethylformamide | colorless prisms |

The asterisk XV shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-phenyl-2,4(1H,3H)-quinazolinone.

The following Examples illustrate the process of the present invention:

#### Example 98

5 The mixture of 5.4 g 1 - (3' - trifluoromethylphenyl) - 2,4(1H,3H) - quinazolinone, 1.3 g dimethylsulfate, and 30 cc acetone was heated for 2 hours at 50—70°C on a water bath, then the solvent was distilled off. The residue was then poured into 20% sodium hydroxide solution under cooling for neutralization, the crystals produced were filtered, washed with water and dried, and, upon recrystallization from ethanol, 4.1 g of colorless prisms of 1 - (3' - trifluoromethylphenyl) - 3 - methyl - 2,4(1H,3H) - quinazolinone were obtained.

melting point  
ultimate

analysis value

theoretical values

found values

189—189.5°C

$C_{16}H_{11}F_3N_2O_3$

C: 60.00 H: 3.46 N: 8.75

C: 60.01 H: 3.66 N: 8.46

#### Example 99

To 5.4 g 1 - (3' - trifluoromethylphenyl) - 2,4(1H,3H) - quinazolinone, and 40 cc dried dimethylformamide was added 1 g of 50% sodium hydride; the mixture was stirred for one hour. Then, 3.6 g ethyl iodide were further added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystalliza-

20

25

30

tion from ethanol, 5 g of colorless prisms of 1 - (3' - trifluoromethylphenyl) - 3 - ethyl - 2,4(1H,3H) - quinazolinedione were obtained.

|   |                           |                          |
|---|---------------------------|--------------------------|
| 5 | melting point<br>ultimate | 156—157°C                |
|   | analysis value            | $C_{17}H_{13}F_3N_2O_2$  |
|   | theoretical values        | C: 61.07 H: 3.92 N: 8.38 |
|   | found values              | C: 61.07 H: 3.98 N: 8.32 |

#### Example 100

10 0.6 g metallic sodium was added to 10 cc 1-butanol and sodium 1-butoxide was formed. To this was added the solution obtained by dissolving 6.5 g 1 - (3' - trifluoromethylphenyl) - 2,4(1H,3H) - quinazolinedione in 20 cc dried dimethylformamide, said solution  
15 mixture was stirred for 1 hour, then 10.5 g of n-butyl bromide were added and the mixture was stirred for 3 hours at room temperature. Water was further added, the crystals produced were filtered and dried, and, upon recrystallization from methanol, 6.1 g of colorless prisms of 1 - (3' - trifluoromethylphenyl) - 3 - (n - butyl) - 2,4(1H,3H) - quinazolinedione were obtained.

|    |                           |                          |
|----|---------------------------|--------------------------|
| 25 | melting point<br>ultimate | 126—127°C                |
|    | analysis value            | $C_{19}H_{17}F_3N_2O_2$  |
|    | theoretical values        | C: 62.98 H: 4.73 N: 7.73 |
|    | found values              | C: 63.39 H: 5.04 N: 7.95 |

#### Example 101

30 0.5 g sodamine was added to the mixture of 3.6 g 1 - (3' - trifluoromethylphenyl) - 2,4 - (1H,3H) - quinazolinedione and 30 cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 5.9 g of isopentyl iodide were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals  
40 produced were filtered and dried, and, upon recrystallization from methanol, 3.9 g of colorless prisms of 1 - (3' - trifluoromethylphenyl) - 3 - (isopentyl) - 2,4(1H,3H) - quinazolinedione were obtained.

|    |                           |                          |
|----|---------------------------|--------------------------|
| 45 | melting point<br>ultimate | 115—115.5°C              |
|    | analysis value            | $C_{20}H_{19}F_3N_2O_2$  |
|    | theoretical values        | C: 63.82 H: 5.09 N: 7.44 |
|    | found values              | C: 63.95 H: 5.18 N: 7.38 |

#### Example 102

50 1 g of 50% sodium hydride was added to the mixture of 5.4 g 1 - (3' - trifluoromethylphenyl) - 2,4(1H,3H) - quinazolinedione and 40 cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 4 g of benzyl bromide were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added

water, the crystals produced were filtered and dried, and, upon recrystallization from methanol, 6 g of colorless prisms of 1 - (3' - trifluoromethylphenyl) - 3 - benzyl - 2,4 - (1H,3H) - quinazolinedione were obtained.

|  |                           |                          |
|--|---------------------------|--------------------------|
|  | melting point<br>ultimate | 183—184°C                |
|  | analysis value            | $C_{22}H_{17}F_3N_2O_2$  |
|  | theoretical values        | C: 66.66 H: 3.81 N: 7.07 |
|  | found values              | C: 66.67 H: 3.90 N: 6.79 |

#### Example 103

70 1.3 g of 50% sodium hydride was added to the mixture of 7 g 1 - (3' - trifluoromethylphenyl) - 2,4(1H,3H) - quinazolinedione and 40 cc dried dimethylformamide, and the mixture was stirred for one hour. Then 4.3 g 1-bromo-2-chloroethane were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered and dried, and, upon recrystallization from methanol, 6.3 g of colorless prisms of 1 - (3' - trifluoromethylphenyl) - 3 - (2'' - chloroethyl) - 2,4(1H,3H) - quinazolinedione were obtained.

|  |                           |                           |
|--|---------------------------|---------------------------|
|  | melting point<br>ultimate | 136—137°C                 |
|  | analysis value            | $C_{17}H_{13}ClF_3N_2O_2$ |
|  | theoretical values        | C: 55.37 H: 3.28 N: 7.60  |
|  | found values              | C: 55.17 H: 3.39 N: 7.50  |

#### Example 104

1 g of 50% sodium hydride was added to the mixture of 5.4 g 1 - (3' - trifluoromethylphenyl) - 2,4(1H,3H) - quinazolinedione and 40 cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 4.5 g diethylaminoethyl chloride were added and the mixture was heated for 3 hours at 40—45°C. The solvent was then distilled under reduced pressure, the residue was added with water, and an oily substance was obtained. Said substance was extracted with ether and, after dehydration, 23% ethanol hydrochloric acid was added under cooling for acidification. Then, the solvent was distilled off under reduced pressure, the residue was recrystallized from ethanol and ethyl acetate, and 6.2 g of colorless prisms of 1 - (3' - trifluoromethylphenyl) - 3 - (2'' - diethylaminoethyl) - 2,4(1H,3H) - quinazolinedione hydrochloride were obtained.

|  |                           |                           |
|--|---------------------------|---------------------------|
|  | melting point<br>ultimate | 229—230°C                 |
|  | analysis value            | $C_{21}H_{23}ClF_3N_3O_2$ |
|  | theoretical values        | C: 57.08 H: 5.25 N: 9.51  |
|  | found values              | C: 57.05 H: 5.47 N: 9.43  |

#### Example 105

2.4 g of 50% sodium hydride were added to the mixture of 9.2 g 1 - (3' - trifluoromethyl-

- phenyl) - 2,4(1H, 3H) - quinazolin-2-one and 80 cc dried dimethylformamide, and the mixture was stirred for one hour. Then, ethylene bromohydrin was added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered and dried, and, upon recrystallization from methyl alcohol, 10 g of colorless prisms of 1 - (3' - trifluoromethylphenyl) - 3 - (2'' - hydroxyethyl) - 2,4(1H, 3H) - quinazolin-2-one were obtained.
- melting point 138—139°C  
ultimate  
analysis value  $C_{17}H_{13}F_3N_2O_2$   
theoretical values C: 58.29 H: 3.74 N: 8.00  
found values C: 58.40 H: 3.71 N: 8.11
- Example 106
- 1 g of 50% sodium hydride was added to the mixture of 5.4 g 1 - (3' - trifluoromethylphenyl) - 2,4(1H, 3H) - quinazolin-2-one and 40 cc dried dimethylformamide, and the mixture was stirred for one hour. Then 3.4 g of chloromethyl ethyl ether were added and the mixture was reacted for 3 hours. The solvent was then distilled off under reduced pressure, the residue was added with water, the crystals produced were filtered and dried, and, upon recrystallization from methyl alcohol, 5 g of colorless prisms of 1 - (3' - trifluoromethylphenyl) - 3 - ethoxymethyl - 2,4(1H, 3H) - quinazolin-2-one were obtained.
- melting point 157.5—159°C  
ultimate  
analysis value  $C_{18}H_{15}F_3N_2O_2$   
theoretical values C: 59.34 H: 4.15 N: 7.69  
found values C: 59.61 H: 4.42 N: 7.58
- Example 107
- 1 g of 50% sodium hydride was added to the mixture of 5.4 g 1 - (3' - trifluoromethylphenyl) - 2,4(1H, 3H) - quinazolin-2-one and 40 cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 6.7 g of 2-bromoethyl acetate were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, the residue was added with water, the crystals produced were filtered and dried, and, upon recrystallization from methyl alcohol, 5.7 g of colorless prisms of 1 - (3' - trifluoromethylphenyl) - 3 - (2'' - acetoxyethyl) - 2,4(1H, 3H) - quinazolin-2-one were obtained.
- melting point 111.5—112°C  
ultimate  
analysis value  $C_{19}H_{16}F_3N_2O_4$   
theoretical values C: 58.16 H: 3.85 N: 7.14  
found values C: 58.28 H: 3.64 N: 7.15
- Example 108
- 0.5 g of 50% sodium hydride was added to the mixture of 2.7 g 1 - (3' - trifluoromethylphenyl) - 2,4(1H, 3H) - quinazolin-2-one and 20 cc dried dimethylformamide, and the mixture was stirred for one hour. Then, a solution obtained by dissolving 3.4 g 1 - (3' - trifluoromethylphenyl) - 3 - monochloromethoxymethyl - 2,4(1H, 3H) - quinazolin-2-one in 20 cc dried dimethylformamide was added and the mixture was reacted for 4 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered and dried, and, upon recrystallization from methyl alcohol and ethyl acetate, 58 g of colorless prisms of bis - [3 - (1 - 3' - trifluoromethylphenyl) - 2,4(1H, 3H) - quinazolin-2-one]-methyl ether were obtained.
- melting point 114—114.5°C  
ultimate  
analysis value  $C_{32}H_{20}F_6N_4O_5$   
theoretical values C: 58.72 H: 3.08 N: 8.56  
found values C: 58.90 H: 2.86 N: 8.57
- Example 109
- 1 g of 50% sodium hydride was added to the mixture of 5.4 g 1 - (3' - trifluoromethylphenyl) - 2,4(1H, 3H) - quinazolin-2-one and 40 cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 4.3 g of 1 - chloro - 2 - (N, N - dimethylcarbamoyloxy)-ethane were added and the mixture was reacted for 4 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water and the residue was held under cooling. The crystals produced were recrystallized from methyl alcohol, and 5.2 g of colorless prisms of 1 - (3' - trifluoromethylphenyl) - 3 - (2'' - N, N - dimethylcarbamoyloxyethyl) - 2,4(1H, 3H)-quinazolin-2-one were obtained.
- melting point 157—158°C  
ultimate  
analysis value  $C_{20}H_{18}F_3N_3O_4$   
theoretical values C: 57.01 H: 4.31 N: 9.97  
found values C: 57.23 H: 4.20 N: 10.0
- Example 110
- 1 g of sodium hydride was added to the mixture of 5.4 g 1 - (3' - trifluoromethylphenyl) - 2,4(1H, 3H) - quinazolin-2-one and 40 cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 4 g of *p*-chlorobenzoyl chloride were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered and dried, and, upon recrystallization from ethanol, 5.7 g of colorless prisms of 1-(3'-trifluoromethylphenyl) - 3 - (4'' - chloro-

benzoyl) - 2,4(1H, 3H) - quinazolinedione were obtained.

melting point 196—197°C  
ultimate

5 analysis value  $C_{22}H_{12}ClF_3N_2O_3$   
theoretical values C: 61.33 H: 3.28 N: 6.50  
found values C: 61.45 H: 3.32 N: 6.33

#### Example 111

10 0.7g of sodium hydride was added to the mixture of 3.1g 1 - (3' - trifluoromethylphenyl) - 2,4(1H,3H) - quinazolinedione and 40cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 2g of acetyl chloride were added dropwise and the  
15 mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered and dried, and, upon recrystallization from methanol, 2.5g of colorless prisms of  
20 1 - (3' - trifluoromethylphenyl) - 3 - acetyl-2,4(1H,3H) - quinazolinedione were obtained.

melting point 165—166°C  
ultimate

25 analysis value  $C_{17}H_{11}F_3N_2O_3$   
theoretical values C: 58.62 H: 3.18 N: 8.05  
found values C: 58.87 H: 3.26 N: 7.91

#### Example 112

30 The mixed solution consisting of 2g 1-(3'-trifluoromethylphenyl) - 2,4(1H,3H) - quinazolinedione, 30cc dried dimethylformamide and 1.6g dried pyridine was heated to 80°C. Then, 4.2g of benzoyl chloride were added dropwise and the mixture was reacted for 3  
35 hours at 80—90°C. It was then filtered, the filtrate was distilled under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystallization from methanol, 1.8g of colorless prisms of 1 - (3' - trifluoromethylphenyl)-  
40 3 - benzoyl - 2,4(1H,3H) - quinazolinedione were obtained.

melting point 166—167°C  
ultimate

45 analysis value  $C_{22}H_{12}F_3N_2O_3$   
theoretical values C: 64.39 H: 3.19 N: 6.83  
found values C: 64.24 H: 3.30 N: 6.87

#### Example 113

50 A mixed solution consisting of 3g 1-(3'-trifluoromethylphenyl) - 2,4(1H,3H) - quinazolinedione, 30cc dimethylformamide and 4g triethylamine was heated to 80°C. Then, 2.8g of propionyl chloride were added dropwise and the mixture was reacted for 3 hours at  
55 80—90°C. It was then filtered, the filtrate was dried by evaporation under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystallization from methanol, 2.8g of colorless

needles of 1 - (3' - trifluoromethylphenyl)-3 - propionyl - 2,4(1H,3H) - quinazolinedione were obtained.

melting point 177.5—178.5°C  
ultimate

65 analysis value  $C_{15}H_{10}F_3N_2O_4$   
theoretical values C: 56.02 H: 3.96 N: 10.32  
found values C: 56.21 H: 3.83 N: 10.24

#### Example 114

The mixture of 5g 1 - (3' - chlorophenyl)-2,4(1H, 3H) - quinazolinedione, 1.3g dimethyl sulfate and 50cc acetone was heated for 2 hours at 50—70°C on a water bath, then the solvent was distilled off, the residue was poured into 20% sodium hydroxide solution under cooling for neutralization, the crystals produced were filtered, washed with water and dried, and, upon recrystallization from dimethylformamide, 4.2g of colorless prisms of  
70 1 - (3' - chlorophenyl) - 3 - methyl - 2,4-(1H, 3H) - quinazolinedione were obtained.

melting point 223—226°C  
ultimate

analysis value  $C_{15}H_{11}ClN_2O_2$   
theoretical values C: 62.84 H: 3.87 N: 9.77  
found values C: 62.75 H: 3.84 N: 9.79  
85

#### Example 115

1g of 50% sodium hydride was added to the mixture of 4.1g 1 - (3' - chlorophenyl)-2,4(1H, 3H) - quinazolinedione and 40cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 3.3g of glycerol- $\alpha$ -monochlorohydrin were added and the mixture was reacted for 1.5 hours at room temperature. The solvent was distilled off under reduced pressure, the residue was added with water, the crystals produced were filtered, and, upon recrystallization from methyl alcohol, 4.2g of colorless needles of 1 - (3' - chlorophenyl) - 3 - (2'', 3'' - dihydroxypropyl)-  
90 2,4(1H, 3H) - quinazolinedione were obtained.

melting point 163—164°C  
ultimate

analysis value  $C_{17}H_{11}ClN_2O_4$   
theoretical values C: 58.88 H: 4.36 N: 8.08  
found values C: 59.08 H: 4.37 N: 8.07  
105

#### Example 116

0.5g of 50% sodium hydride was added to the mixture of 1.5g 1 - (2', 3' - dichlorophenyl) - 2,4(1H,3H) - quinazolinedione and 30cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 5g of 2-bromoethyl acetate were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were then recrystallized from ethanol, and 1.7g of colorless needles of 1 - (2', 3' - dichlorophenyl) - 3-  
110  
115

- (2'' - acetoxyethyl) - 2,4(1H,3H) - quinazolin-  
edione were obtained.
- melting point 183.5—184.5°C  
ultimate  
5 analysis value  $C_{18}H_{14}Cl_2N_2O_4$   
theoretical values C: 54.98 H: 3.59 N: 7.13  
found values C: 55.00 H: 3.53 N: 7.14
- Example 117
- 0.6g metallic sodium was added to 10cc  
10 ethyl alcohol, and sodium ethoxide was  
formed. Then, a solution obtained by dis-  
solving 5.8g of 1 - (2' - chlorophenyl) - 2,4-  
(1H,3H) - quinazolin-3-one in 20ml dried  
15 dimethylformamide was added. Further, 6.6g  
of ethyl iodide were added and reaction was  
allowed to take place for 3 hours at room  
temperature. Then, water was added, the  
crystals produced were filtered and dried, and,  
upon recrystallization from methyl alcohol,  
20 5.4g of colorless prisms of 1 - (2' - chloro-  
phenyl) - 3 - ethyl - 2,4(1H, 3H) - quinazo-  
lin-3-one were obtained.
- melting point 145—146°C  
ultimate  
25 analysis value  $C_{16}H_{10}ClN_2O_2$   
theoretical values C: 63.90 H: 4.36 N: 9.31  
found values C: 63.96 H: 4.27 N: 9.42
- Example 118
- 0.7g of 50% sodium hydride was added to  
30 the mixture of 2.7g 1 - (4' - chlorophenyl)-  
2,4(1H, 3H) - quinazolin-3-one and 30cc dried  
dimethylformamide, and the mixture was  
stirred for one hour. Then, 3.6g of 3-di-  
35 methylamino - propyl chloride were added and  
the mixture was reacted for 3 hours at room  
temperature. The solvent was distilled under  
reduced pressure, to the residue was added  
water, the crystals produced were filtered, and,  
upon recrystallization from methyl alcohol,  
40 2.9g of colorless needles of 1 - (4' - chloro-  
phenyl) - 3 - (3'' - dimethylaminopropyl)-  
2,4(1H, 3H) - quinazolin-3-one were obtained.
- melting point 164.5—165.5°C  
ultimate  
45 analysis value  $C_{19}H_{20}ClN_2O_2$   
theoretical values C: 63.77 H: 5.63 N: 11.74  
found values C: 63.62 H: 5.65 N: 11.50
- Example 119
- 1.1g sodamide were added to the mixture of  
50 4.5g 1 - (3', 4' - dichlorophenyl) - 2,4(1H,  
3H) - quinazolin-3-one and 40 ml dimethyl-  
formamide, and the mixture was stirred for  
one hour. Then 7.3g of ethyl bromoacetate  
were added and the mixture was reacted for  
55 one hour. The solvent was then distilled off  
under reduced pressure, to the residue was  
added water, the crystals produced were fil-  
tered, and, upon recrystallization from the  
mixed solvent consisting of dimethylform-
- amide and ethanol, 4.6g of colorless prisms  
of ethyl 1 - (3', 4' - dichlorophenyl) - 2,4-  
(1H,3H) - quinazolin-3-one 3-acetate were  
obtained.
- melting point 157.5—158.5°C  
ultimate  
65 analysis value  $C_{18}H_{14}Cl_2N_2O_4$   
theoretical values C: 54.98 H: 3.59 N: 7.12  
found values C: 54.93 H: 3.53 N: 7.06
- Example 120
- 0.6g of 50% sodium hydride was added to  
70 the mixture of 1.7g 1 - (2', 6' - dichloro-  
phenyl) - 2,4(1H,3H) - quinazolin-3-one and  
30cc dried dimethylformamide, and the mix-  
ture was reacted for one hour at room tem-  
pera. Then, 5g of ethyl iodide were added,  
75 and the mixture was further reacted for two  
hours at room temperature. Then, the solvent  
was distilled off under reduced pressure, to the  
residue was added water, the crystals pro-  
duced were filtered, and, upon recrystallization  
80 from methanol, 1.5 g of colorless prisms of  
1 - (2', 6' - dichlorophenyl) - 3 - ethyl - 2,4-  
(1H,3H) - quinazolin-3-one were obtained.
- melting point 174.5—175.5°C  
ultimate  
85 analysis value  $C_{16}H_{12}Cl_2N_2O_2$   
theoretical values C: 57.33 H: 3.61 N: 8.36  
found values C: 57.43 H: 3.49 N: 8.43
- Example 121
- 0.8g of 50% sodium hydride was added to  
90 the mixture of 3g 1 - (3' - fluorophenyl)-  
2,4(1H,3H) - quinazolin-3-one and 30cc dried  
dimethylformamide, and the mixture was  
stirred for one hour. Then, 3.7g of ethylene  
95 bromohydrin were added and the mixture was  
reacted for 3 hours at room temperature. The  
solvent was then distilled off under reduced  
pressure, to the residue was added water, the  
crystals produced were then recrystallized  
100 from the mixed solvent consisting of meth-  
anol, and water, and 2.9g of colorless prisms  
of 1 - (3' - fluorophenyl) - 3 - (2'' - hydroxy-  
ethyl) - 2,4(1H,3H) - quinazolin-3-one were  
obtained.
- melting point 136.5—137.5°C  
ultimate  
105 analysis value  $C_{16}H_{13}FN_2O_3$   
theoretical values C: 63.99 H: 4.46 N: 9.33  
found values C: 64.15 H: 4.07 N: 9.37
- Example 122
- The mixture of 1.8g 1 - (4' - fluorophenyl)-  
2,4(1H,3H) - quinazolin-3-one, 3g diethyl  
sulfate and 50cc acetone was heated for 2  
hours at 50—70°C on a waterbath. The sol-  
vent was then distilled off, the residue was  
115 poured into 20% sodium hydroxide solution  
under cooling for neutralization, the crystals  
produced were filtered and washed with water,

and, upon recrystallization from the mixed solvent consisting of methanol and dimethylformamide, 1.6g of colorless prisms of 1-(4'-fluorophenyl) - 3 - ethyl - 2,4(1H,3H) - quinazolidione were obtained.

melting point 213—215°C  
ultimate  
analysis value  $C_{16}H_{13}FN_2O_2$   
theoretical values C: 67.60 H: 4.61 N: 9.85  
found values C: 67.51 H: 4.38 N: 9.91

#### Example 123

0.7g of 50% sodium hydride was added to the mixture of 1.8g 1 - (4' - fluorophenyl)-2,4(1H,3H) - quinazolidione and 30cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 3.2g of 2-bromoethyl ethyl ether were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystallization from the mixed solvent consisting of methanol and water, 1.8g of colorless needles of 1 - (4' - fluorophenyl) - 3-(2'' - ethoxyethyl) - 2,4(1H,3H) - quinazolidione were obtained.

melting point 112—113°C  
ultimate  
analysis value  $C_{15}H_{11}FN_2O_2$   
theoretical values C: 65.85 H: 5.22 N: 8.53  
found values C: 65.79 H: 5.34 N: 8.64

#### Example 124

0.4g of 50% sodium hydride was added to the mixture of 2g 1 - (3' - bromophenyl)-2,4(1H,3H) - quinazolidione and 30cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 5g of 2-bromoethyl acetate were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystallization from methanol, 1.8g of colorless prisms of 1 - (3' - bromophenyl) - 3-(2'' - acetoxyethyl) - 2,4(1H,3H) - quinazolidione were obtained.

melting point 145—146°C  
ultimate  
analysis value  $C_{15}H_{11}BrN_2O_4$   
theoretical values C: 53.61 H: 3.75 N: 6.95  
found values C: 53.46 H: 3.71 N: 6.80

#### Example 125

0.6g metallic sodium was added to 10ml ethanol and sodium ethoxide was formed. Then, a solution obtained by dissolving 5.3g 1 - (2',3' - dimethylphenyl) - 2,4(1H,3H) quinazolidione in 20cc dried dimethylformamide was added. Further, 4.6g of ethyl iodide were added, and the mixture was reacted for

3 hours at room temperature. Then, water was added, the crystals produced were filtered, and, upon recrystallization from methanol, 4.7g of colorless needles of 1 - (2',3' - dimethylphenyl) - 3 - ethyl - 2,4(1H,3H) - quinazolidione were obtained.

melting point 202—205°C  
ultimate  
analysis value  $C_{18}H_{18}N_2O_2$   
theoretical values C: 73.45 H: 6.16 N: 9.52  
found values C: 72.80 H: 5.93 N: 9.64

#### Example 126

0.5g of 50% sodium hydride was added to the mixture of 1.5g 1 - (3' - methoxyphenyl)-2,4(1H,3H) - quinazolidione and 30cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 5g of 2-bromoethylacetate were added and the mixture was reacted for 3 hours at room temperature. The solvent was distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystallization from methanol, 1.8g of colorless prisms of 1 - (3' - methoxyphenyl) - 3-(2'' - acetoxyethyl) - 2,4(1H,3H) - quinazolidione were obtained.

melting point 130—131°C  
ultimate  
analysis value  $C_{18}H_{18}N_2O_5$   
theoretical values C: 64.40 H: 5.12 N: 7.91  
found values C: 64.52 H: 4.96 N: 7.85

#### Example 127

0.2g of sodamide was added to the mixture of 1g 1 - (4' - ethoxyphenyl) - 2,4(1H,3H)-quinazolidione and 20cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 1.9g of 1 - bromo - 2 - chloroethane were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystallization from methanol, 1.0g of colorless needles of 1 - (4' - ethoxyphenyl) - 3-(2'' - chloroethyl) - 2,4(1H,3H) - quinazolidione was obtained.

melting point 144—146°C  
ultimate  
analysis value  $C_{18}H_{17}ClN_2O_3$   
theoretical values C: 62.70 H: 4.97 N: 8.12  
found values C: 62.66 H: 4.96 N: 8.25

#### Example 128

0.6g of 50% sodium hydride was added to the mixture of 2.4g 1 - phenyl - 2,4(1H,3H) - quinazolidione and 30cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 6.8g of 2-bromoethyl benzoate were added and the mixture was reacted for 3 hours at room temperature.

- The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were then recrystallized from the mixed solvent consisting of dimethylformamide and methanol, and 3.9g of 1 - phenyl - 3 - (2'' - benzoyloxyethyl) - 2,4(1H,3H) - quinazolidinedione were obtained.

|    |                    |   |
|----|--------------------|---|
|    | melting point      | 150.5—151°C.  |
|    | ultimate           |   |
| 10 | analysis value     | C <sub>23</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub> |
|    | theoretical values | C: 71.49 H: 4.70 N: 7.25                                      |
|    | found values       | C: 71.41 H: 4.79 N: 7.35                                      |

#### Example 129

- 2.8g of propionyl chloride were added dropwise to the mixed solution consisting of 5.6g 1 - phenyl - 2,4(1H,3H) - quinazolidinedione, 30cc dried dimethylformamide and 4g triethylamine, and the mixture was reacted for 3 hours at 80—90°C. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystallization from methanol, 2.3g of colorless needles of 1 - phenyl - 3 - propionyl - 2,4(1H,3H) - quinazolidinedione were obtained

|    |                    |   |
|----|--------------------|---|
|    | melting point      | 154—155°C   |
|    | ultimate           |   |
|    | analysis value     | C <sub>17</sub> H <sub>11</sub> N <sub>2</sub> O <sub>3</sub> |
|    | theoretical values | C: 69.37 H: 4.79 N: 9.52                                      |
| 30 | found values       | C: 69.21 H: 4.87 N: 9.31                                      |

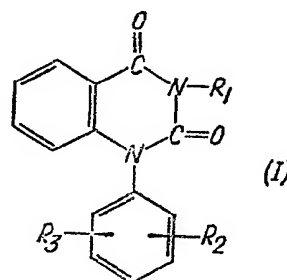
#### Example 130

- 0.7g of 50% sodium hydride was added to the mixture of 1.9g 1 - (3' - methylphenyl) - 2,4(1H,3H) - quinazolidinedione and 30cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 3g of ethylene bromohydrin were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystallization from the mixed solvent consisting of methanol and water, 1.9g of colorless prisms of 1 - (3' - methylphenyl) - 3 - (2'' - hydroxyethyl) - 2,4(1H,3H) - quinazolidinedione were obtained.

|    |                    |   |
|----|--------------------|---|
|    | melting point      | 152—154°C   |
|    | ultimate           |   |
|    | analysis value     | C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> |
| 50 | theoretical values | C: 68.91 H: 5.44 N: 9.45                                      |
|    | found values       | C: 68.74 H: 5.24 N: 9.45                                      |

#### WHAT WE CLAIM IS:—

1. Compounds of formula:



wherein R<sub>1</sub> represents an alkyl, a substituted alkyl or an acyl radical; R<sub>2</sub> and R<sub>3</sub> each represent a hydrogen atom, a CF<sub>3</sub> group, a Cl, Br, or F atom, or a methyl, methoxy or ethoxy radical.

2. Compounds of formula I, as defined in Claim 1 wherein R<sub>2</sub> represents a trifluoromethyl group and R<sub>3</sub> represents a hydrogen atom.

3. Compounds of formula I, as defined in Claim 1 wherein R<sub>2</sub> represents a chlorine atom and R<sub>3</sub> represents a hydrogen atom.

4. Compounds of formula I, as defined in Claim 1, wherein R<sub>2</sub> and R<sub>3</sub> each represent a chlorine atom.

5. Compounds of formula I, as defined in Claim 1, wherein R<sub>2</sub> represents a fluorine atom and R<sub>3</sub> represents a hydrogen atom.

6. Compounds of formula I, as defined in Claim 1, wherein R<sub>2</sub> represents a bromine atom and R<sub>3</sub> represents a hydrogen atom.

7. Compounds of formula I, as defined in Claim 1, wherein R<sub>2</sub> and R<sub>3</sub> each represent a methyl group.

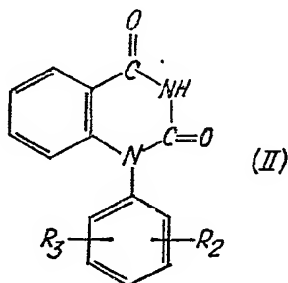
8. Compounds of formula I, as defined in Claim 1, wherein R<sub>2</sub> represents a methoxy group and R<sub>3</sub> represents a hydrogen atom.

9. Compounds of formula I, as defined in Claim 1, wherein R<sub>2</sub> represents an ethoxy group and R<sub>3</sub> represents a hydrogen atom.

10. Compounds of formula I, as defined in Claim 1, wherein R<sub>2</sub> and R<sub>3</sub> each represent a hydrogen atom.

11. Compounds of formula I, as defined in Claim 1, wherein R<sub>2</sub> represents a methyl group and R<sub>3</sub> represents a hydrogen atom.

12. A process for preparing compounds of formula I, as defined in Claim 1, which comprises reacting a compound of formula:



wherein  $R_2$  and  $R_3$  are as defined in Claim 1, with an alkylating or acylating agent containing the group  $R_1$ , as defined in Claim 1.

5 13. A process as claimed in Claim 12, wherein said alkylating or acylating agent is a compound having the general formula  $R_1X$  in which X represents a halogen atom.

10 14. A process as claimed in Claim 12, wherein said alkylating agent is a compound of formula  $(R)_2SO_4$  in which R represents a methyl or ethyl group.

15 15. A process as claimed in any of Claims 12 to 14, wherein the reaction is effected in the presence of a sodium alcoholate, sodamide, sodium hydride; an organic base or an inorganic base.

16. A process as claimed in Claim 15, wherein the organic base comprises pyridine or a trialkylamine.

20 17. A process as claimed in Claim 15,

wherein the inorganic base comprises at least one alkali metal hydroxide or alkali metal carbonate.

18. A process as claimed in any of Claims 12 to 17, wherein the reaction is effected in an organic solvent.

19. A process as claimed in Claim 18, wherein said organic solvent comprises acetone or dimethylformamide.

20. Pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I, as defined in Claim 1, in association with at least one pharmaceutically acceptable vehicle, diluent, excipient, or carrier.

21. Compounds of formula I, as defined in Claim 1, whenever prepared by a process as claimed in any of Claims 12 to 19.

22. A process for producing quinazolinone derivatives substantially as herein described with reference to any one of the Examples given.

23. Compounds of formula I, as defined in Claim 1, substantially as herein described with reference to any of Examples 1 to 97.

24. Pharmaceutical compositions as claimed in Claim 20, substantially as herein described.

CLEVELAND & JOHNSON,  
Chartered Patent Agents,  
Agents for the Applicants,  
Chancery House, Chancery Lane,  
London WC2A 1QU.